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Budesonide reverses lung hyperinflation in childhood asthma: a controlled study

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Abstract

It was investigated whether inhaled budesonide reduces lung volumes in a group of asthmatic children with lung hyperinflation. Budesonide (800 μg bid, for 2 months) was administered to 12 asthmatic children (mean age, 11.2 ± 3.3 years) with lung hyperinflation (TGV $\geq$ 130% predicted and/or RV $\geq$ 140% predicted) in a randomised, placebo controlled, double blind, crossover study. Body plethysmography (panting frequency controlled at $1 \cdot s^{-1}$) was performed at the beginning, 2 months afterwards (before crossover) and at the end of the study. Budesonide significantly reduced TGV (2.35 ± 0.90 l BTPS or 126 ± 24% predicted) compared with placebo (2.54 ± 1.08 l BTPS, $P = 0.014$ or 140 ± 21% predicted, $P < 0.05$). In addition, budesonide significantly increased mean specific conductance (0.06 ± 0.02 cm H_2O^{-1} l s^{-1} to 0.07 ± 0.01 cm H_2O^{-1} l s^{-1}, $P < 0.05$). It was concluded that budesonide reduced lung hyperinflation most likely by decreasing airway inflammation.

Keywords: Asthma; Lung hyperinflation; Bronchial inflammation; Budesonide

1. Introduction

In a clinical context, hyperinflation implies an abnormal increase in the volume of gas in the lungs at the end of tidal expiration [1]. However, when it was attempted to relate hyperinflation with the airway narrowing occurring in asthma, the picture is much less defined as suggested in a recent review [2] which states that, in this context, there is no clear definition of hyperinflation and of its underlying mechanisms. The authors suggest that both altered properties of airways and lung parenchyma are involved in the development of hyperinflation and point to the importance of measuring residual volume (RV), thoracic gas volume (TVG) and total lung capacity (TLC) to understand the underlying pathophysiological mechanisms.

During an acute attack of asthma [3] there is an increase in all lung volumes which is due not only to the expiratory flow limitation but also to the persistent inspiratory muscle contraction throughout expiration, caused by a reflex mechanism from the constricted airways, which increases end-expiratory volume and produces hyperinflation [4–7]. On the other hand, chronic increases of functional residual capacity (FRC), RV and occasionally of TLC can be observed in some asthmatic patients away from the exacerbations of asthma [2,8] but the mechanisms responsible for these changes, such as loss of bronchial-to-parenchyma interdependence, are still under discussion. A prior study performed in seven asthmatic patients, found a decrease in FRC after a week of systemic steroids that was attributed to an improvement of lung elastic recoil [9] as was later demonstrated [10].

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Although it is accepted that the treatment with steroids reduces inflammation both in the airways and in the parenchyma [11,12], the authors were not aware of any study relating such treatment with measurements of lung volumes that are dependent, amongst other factors, upon lung elastic recoil. In order to do that, an inhaled steroid was given to a group of hyperinflated asthmatic children and lung volumes were monitored in a controlled study.

2. Material and methods

2.1. Study subjects

Patients were selected from all asthmatics that have performed lung function tests in an Allergy Clinic during 1 year. From these, 13 children with asthma and lung hyperinflation, aged 6–18 years old were included. The diagnosis of asthma was made according to accepted criteria [13]. All patients were free from inhaled and systemic steroids and from an exacerbation of asthma for at least 6 weeks before the beginning of the study. During the study period all patients were only taking inhaled budesonide regularly and a short-acting β_2 agonist in a prn basis.

According to their clinical symptoms and/or to daily medication required, 11 patients were classified as having moderate persistent asthma, whereas two were labelled as mild persistent [14]. Symptoms of asthma were detected for the first time, in average, since 8.5 ± 4.2 years ago, with a range between 3.1 and 17.3 years. Chronic lung hyperinflation was considered whenever TGV was repeatedly (in three different occasions during the previous year) equal or higher than 130% predicted [15] and/or RV was equal or higher than 140% predicted [16]. The predicted values were calculated from Zapletal equations [17].

2.2. Study design

The study was performed in two phases (Phase 1 and Phase 2), with a duration of 4 months. It was a controlled study, double blind, against placebo according to randomisation in two groups (G1 and G2) of six patients each. A crossover was done at the end of Phase 1. Budesonide (400 μg $dose^{-1}$) or placebo was administered to each patient through a Turbohaler® device twice a day. The content of the inhaler was blinded both to patients and investigators. Lung volumes were measured three times during the study — before starting budesonide (day 0), at crossover (day 57) and at the end of the study (day 113). Patients were instructed to avoid taking β_2 agonists during the 12-h period preceding the lung function measurements. An informed consent was obtained from the tutors in every case and the study was approved by the Hospital Ethics Committee.

2.3. Methods

A body plethysmograph MasterLab Jaeger (Würzburg, Germany) was used to measure lung volumes (TGV, RV and TLC) and specific conductance (sG_{aw}) according to the method described by Ref. [18]. The procedure followed during measurements was that recommended by the European Respiratory Society [19]. Nevertheless, panting frequency was settled at 1 Hz, using a tachometer as a biofeedback signal to the patient, because lung volumes measured by body plethysmography with high panting frequencies are overestimated in asthma [20,21].

2.4. Analysis

The key questions addressed in this study were: did budesonide modify lung volumes (TGV, RV and TLC) and sG_{aw}, compared with placebo? Did lung volumes correlate with airway calibre before and after treatment with budesonide?

Analysis of variance was used to evaluate the effects of budesonide and placebo according to the methods described in Ref. [22]. Each analysis was tested for period effect and for the presence of carry-over. Delta lung volumes (lung volumes after budesonide — lung volumes after placebo) were correlated with delta conductance (G_{aw}).

3. Results

3.1. Patient characteristics

Distribution by age and sex of the children included in this study is shown on Table 1. One of the patients was excluded because he had an asthma attack treated with oral steroids during placebo phase. For this reason only 12 patients concluded the study. This group had the following mean baseline volumes (Table 2): TGV, 2.7 ± 1.10 l ($141 \pm 21\%$ pred.); RV, 1.59 ± 0.80 l ($170 \pm 53\%$ pred.); and TLC, 4.52 ± 1.62 l ($118 \pm 13\%$ pred.).

3.2. Effect of budesonide on lung volumes

When compared with placebo, only TGV was significantly reduced ($P < 0.05$) after 2 months of inhaled budesonide, from 2.54 ± 1.08 to 2.35 ± 1.08 l. There were no differences between basal volumes and volumes after placebo (Fig. 1).

3.3. Effect of budesonide on airway calibre

As patients were evaluated through body plethysmography, only resistance (or its reciprocal-conductance) was measured. Specific conductance (sG_{aw}) after 2 months of budesonide increased significantly ($P < 0.05$) when compared with sG_{aw} after placebo (from 0.06 ± 0.02 to 0.07 ± 0.01 cm $H_2O^{-1} \cdot l \cdot s^{-1}$, Fig. 1). This increase corresponds to a 17% variation.

3.4. Relation between lung volumes and airway calibre

Delta TGV (as defined in Section 2) was significantly correlated with delta G_{aw} ($r = -0.78$, $P < 0.005$, Fig. 2).

4. Discussion

With this study it has been shown, in a group of 12 young asthmatics with lung hyperinflation, that TGV but not RV or TLC decreased significantly after treatment with an inhaled steroid. This was shown through a double blind, placebo controlled, crossover design.

The reduction of TGV after treatment with budesonide implies that the anti-inflammatory medication reduced end-expiratory volume. Based on the inflammatory theory of asthma, it was hypothesised that this was due, not only to an increase in airway calibre [23–25], but also to a reduction in peribronchial and alveolar inflammation [26] which, when present, causes

Table 1
Characteristics of the asthmatic children with lung hyperinflation studied[a]

No.	Age	Sex	TGV		RV		TLC	
			l	% Pred	l	% Pred	l	% Pred
1	11	F	2.22	120	1.36	144	3.93	105
2	15	M	4.40	163	2.84	244	6.74	124
3	8	M	1.87	133	1.03	142	3.42	118
4	13	F	3.64	181	2.47	243	5.31	130
5	10	M	2.51	127	1.56	168	4.69	116
6	10	M	2.68	146	0.97	110	3.83	102
7	8	F	1.92	129	1.26	161	3.64	120
8	7	M	1.60	130	0.96	146	3.01	119
9	18	M	4.78	177	3.17	272	7.99	147
10	9	F	1.35	122	0.88	147	2.65	117
11	11	M	2.17	132	0.99	122	3.36	99
12	14	M	3.22	131	1.58	146	5.70	114
Mean	12	9M/4F	2.70	141	1.59	170	4.52	118
S.D.	3	–	1.10	21	0.80	53	1.62	13

[a] M, male; F, female; % Pred, % predicted values; S.D., standard deviation.

Table 2
sG_{aw} evolution of asthmatic children with lung hyperinflation during the study[a]

No.	Basal		After placebo		After budesonide	
	cm H_2O^{-1} l s^{-1}	% Pred	cm H_2O^{-1} l s^{-1}	% Pred	cm H_2O^{-1} l s^{-1}	% Pred
1	0.082	90	0.067	74	0.082	90
2	0.03	48	0.067	108	0.076	123
3	0.06	50	0.076	63	0.081	68
4	0.028	33	0.047	56	0.062	74
5	0.041	48	0.079	92	0.066	77
6	0.091	99	0.089	97	0.082	89
7	0.05	44	0.049	43	0.065	57
8	0.072	52	0.059	43	0.08	58
9	0.053	85	0.039	63	0.056	90
10	0.063	41	0.028	18	0.06	39
11	0.066	64	0.05	49	0.059	57
12	0.088	128	0.065	94	0.091	132
Mean	0.060	65	0.060	67	0.072*	79*
S.D.	0.021	29	0.018	27	0.012	27

[a] % Pred, % predicted values; S.D., standard deviation.
* $P < 0.05$ when compared with post placebo.

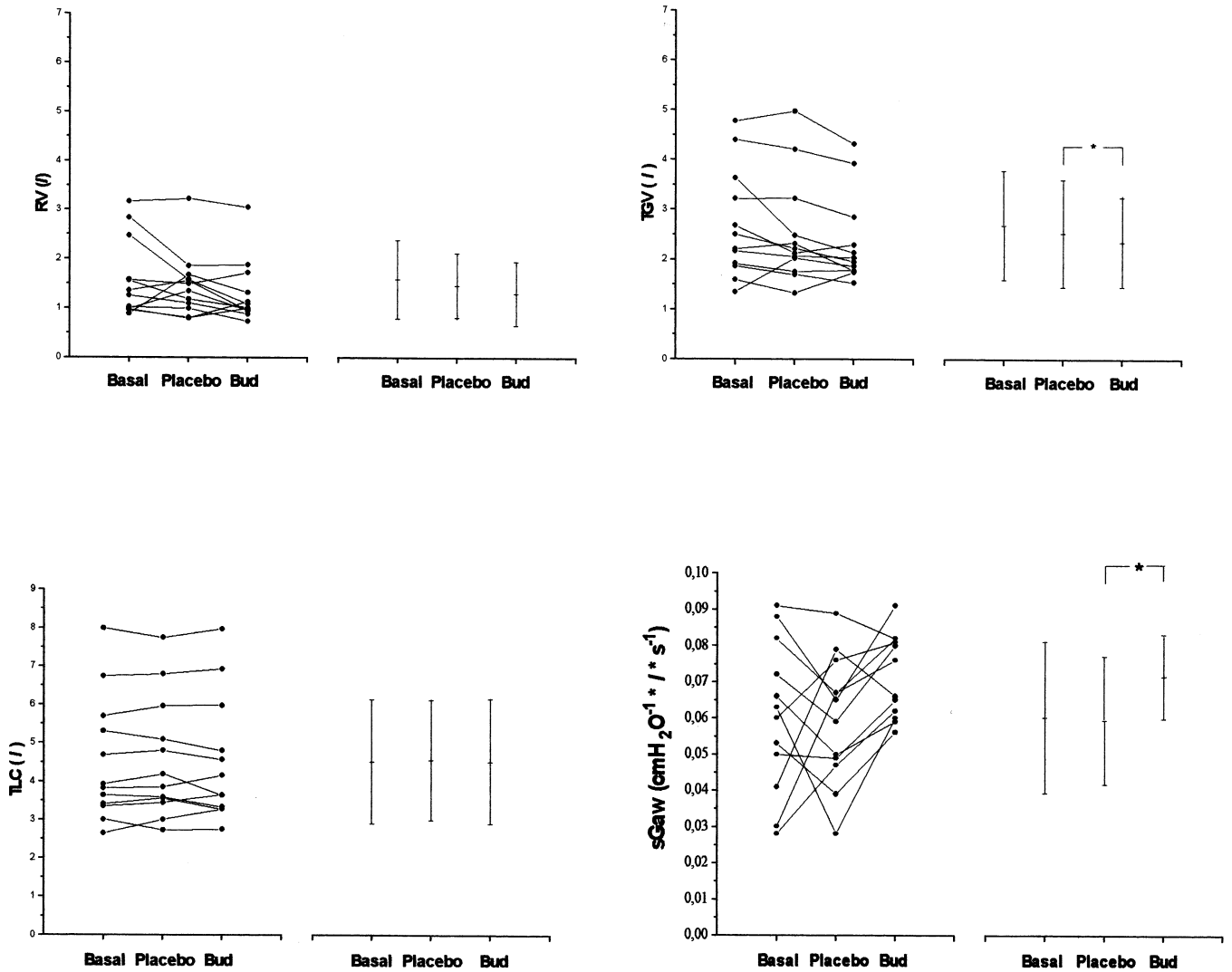

Fig. 1. Comparison of lung volumes (residual volume (RV), upper left panel; thoracic gas volume (TGV), upper right panel; total lung capacity (TLC), lower left panel) and of specific conductance (sG_{aw}) before budesonide or placebo (basal), after placebo (placebo) and after budesonide (Bud) treatment of asthmatic children with lung hyperinflation. On the left hand side of each graphic is represented the individual variation. On the right hand side is represented the mean variation ($\pm$ standard variation); * $P < 0.05$.

a temporary loss of the relationship between small bronchi and parenchyma, thus reducing elastic recoil [27,28]. This is suggested in this study by the fact that a small improvement in airway calibre after budesonide, demonstrated by the increase in sG_{aw}, was not accompanied by a change in RV, which remained higher and not different from placebo. This probably means that a higher RV depends not only on airway calibre but also on persistent parenchymal changes such as a reduction in lung elastic recoil that also contributes to the expiratory flow limitation. Similar observations were made by Şekerel et al. [8] who found a reduction of TLC after 8 weeks of treatment with budesonide, 400 μg day^{-1}.

A recent study [29] has shown that, in chronic stable asthma, lung volumes assessed by measurements of TLC, can be larger than predicted at the start of adolescence and suggested that this change was due to the mitogenic effect of inflammatory mediators which stimulated alveolar multiplication during childhood. This hypothesis is different from a previous one [30] which explained the hyperinflation in chronic asthmatics by a process of alveolar destruction because of the stretching caused by the trapped gas. In this regard it is interesting to note that the younger cases, also at the beginning of adolescence, had higher baseline values of TLC than the older patients, a finding which agrees with the above mentioned hypothesis. The authors are aware that the measurement of TLC by plethysmography can produce methodological errors, however, they were minimised by a panting frequency < 1 Hz. So it was confirmed, as others, that TLC is increased in some of these patients with asthma, whether this is caused by

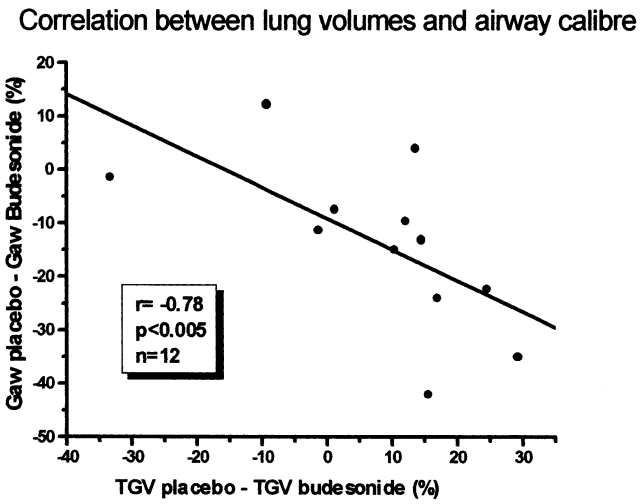

Fig. 2. Graphic representation of the statistically significant correlation between delta thoracic gas volume (TGV) and delta G_{aw} (before and after budesonide) of asthmatic children with lung hyperinflation.

a higher rate of alveolar multiplication or by remodelling of lung tissues or both it is not yet clear.

Another explanation for the increase in TLC could be related to an increase in respiratory muscle strength in chronic asthmatics due to the persistent tonic activity of the inspiratory muscle during expiration. Since respiratory pressures have not been measured, the involvement of the respiratory muscles on the genesis of hyperinflation cannot be excluded, although these changes are considered less likely than those of lung parenchyma. However, the authors' research findings [31], have shown that, at least maximal mouth pressures are similar in children and adolescents with asthma and a group of age matched controls.

The results show that an inhaled steroid, budesonide, can decrease lung volumes in a group of young asthmatics with lung hyperinflation. This reduction in lung volumes was closely related with the increase of airway calibre thus suggesting a major role of airway inflammation in the genesis of chronic lung hyperinflation in asthma.

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